ABSTRACT OF THE INVENTION

The present invention provides methods and compositions for enhancing channel activity to the mutant cystic fibrosis trans-membrane conductance regulator protein (CFTR). The compositions of the invention comprise polypeptides containing CFTR sub-domains that are designed to mimic the folding defect of the full length mutant CFTR proteins, resulting in competitive binding to cytoplasmic chaperones such as Hsc/Hsp70 and Hdj2. The methods of the invention comprise transduction, or recombinant expression, of CFTR polypeptides in a cell expressing mutant CFTR. The presence of the CFTR polypeptide results in a dominant effect whereby the CFTR polypeptide competes with the endogenously expressed mutant CFTR for binding to cytoplasmic chaperones such as Hsc/Hsp70 and Hdj2. Mutant CFTR proteins include, but are not limited to, ΔF508 CFTR. The present invention is based on the discovery that reduced binding of cytoplasmic chaperones to the endogenous ΔF508 CFTR, mediated by the presence of CFTR polypeptides, results in restoration of plasma membrane localization and channel activity. The methods and compositions of the invention can be used to restore channel activity in cystic fibrosis subjects carrying genetic defects in the CFTR gene, such as for example, ΔF508 CFTR.